Clinicopathologic Conference

Malignant Hypertension and Asymmetric Septal Hypertrophy in a 43-Year-Old Black Man

Discussants
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Moderator
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JOSEPH SILVA, JR, MD:* *Discovering the cause of hypertension in any given patient may be confounding to a clinician. The diagnostic evaluation can be simple and inexpensive, or labor-intensive and costly. The evaluation is sometimes not as rigorous as that used for other illnesses. This shortcoming is related in part to the cause of hypertension being relegated to the categories of either essential or renovascular. The patient discussed here was selected because the results of the history and physical examination show that these elements may provide clues in the workup of these patients. In addition, important clinical deductions can be made from preliminary laboratory data to better characterize the cause of hypertension. Dr John Rutledge is Director of the Hypertension Clinic at the University of California Davis Medical Center and will discuss this case. Dr Eng will present the case.*

Case Presentation

ALVIN ENG, MD:† The patient is a 43-year-old black man with a one-year history of hypertension and glucose intolerance treated with hydrochlorothiazide and triamterene (Dyazide) and oral hypoglycemic agents. Two days before admission his regimen was changed to insulin. While at work, he noted a severe occipital headache unrelieved by acetaminophen. He had had no alterations in mental state, dizziness, visual changes, paralysis, weakness or paresthesias. He left work early and went to bed. He was found the next morning by his fiancée to be extremely lethargic, confused and dysarthric and was brought to the emergency room where he was given an infusion of 50% glucose solution, thiamine and naloxone, without effect. No history of recent illnesses, alcohol abuse, smoking or intravenous drug abuse was obtained. Present medications were Dyazide, one tablet twice a day, and insulin.

On physical examination he was awake but lethargic and offered no complaints. His temperature was 34.4°C (94°F) and blood pressure was 166/104 mm of mercury. Heart rate and respiratory rate were 64 and 12 per minute, respectively. Examination of the head, eyes, ears, nose and throat showed no abnormalities. The skin showed no abnormalities. The lungs were normal to auscultation and percussion. On cardiovascular examination there were no murmurs, gallops, rubs or clicks. The abdomen was nontender and without organomegaly. Pulses were equal and brisk. Neurologic examination revealed no focal or lateralizing signs.

Laboratory examination elicited the following: hemoglobin 15.6 grams per dl, leukocyte count 7,100 per μl. Serum chemistry values were sodium 133, potassium 3.1, chloride 96 and carbon dioxide 28 mEq per liter; creatinine 0.8, glucose 160 and calcium 9.5 mg per dl. A chest roentgenogram was unremarkable. An electrocardiogram showed a sinus rhythm, a rate of 60, axis +45 degrees, normal intervals and a probable U wave (Figure 1). Urinalysis showed a specific gravity of 1.006, pH 6.0 and 0 to 2 leukocytes per high powered field. Serum and urine toxicology screens were negative.

Hospital Course

The patient was admitted to the medical intensive care unit for evaluation of hypothermia. His blood pessure on arriving at the unit was 260/160 mm of mercury with a sinus tachycardia of 150 beats per minute. A new grade 3/6 crescendo-decrescendo systolic murmur was now audible at the apex and

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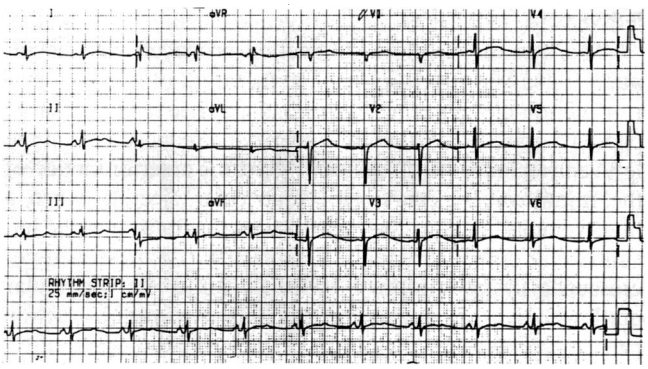

Figure 1.—A 12-lead electrocardiogram shows U waves in leads II, III, aV_F and V_{4-6}.

radiated throughout the precordium and neck. The murmur increased during Valsalva's maneuver and diminished with isometric exercise and squatting. An echocardiogram showed normal valves and wall motion, but systolic anterior motion of the mitral valve was present. Left ventricular dimensions were as follows: left ventricular end-diastolic diameter 4.1 cm (normal 3.5 to 5.7), interventricular septum 2.8 cm (normal 0.6 to 1.1) and posterior wall thickness 1.5 cm (normal 0.6 to 1.1).

Three doses of hydralazine hydrochloride, 10 mg, were given intramuscularly without effect. A sodium nitroprusside infusion and propranolol hydrochloride, 20 mg by mouth, did not cause a significant reduction in blood pressure. Administering verapamil, 5 mg intravenously, resulted in hypotension (70/40 mm of mercury). The blood pressure stabilized at 150/90 mm of mercury after fluid resuscitation and 15 minutes later rose to 240/130 mm of mercury. Sodium nitroprusside was titrated up to 6 μg per kg per minute with gradual lowering of the blood pressure to 140/70 mm of mercury. A total of 1.5 mg digoxin was given intravenously to reduce the heart rate to 90 to 110 beats per minute. Because of the presence of asymmetric septal hypertrophy, metoprolol tartrate, 5 mg, was given intravenously with elevation of the blood pressure to 220/140 mm of mercury and the sodium nitroprusside dosage was again increased to lower the blood pressure.

Further diagnostic studies were initiated.

Discussion

JOHN C. RUTLEDGE, MD:* To summarize the salient features of this case, the patient is a middle-aged black man with a one-year history of hypertension and diabetes mellitus with a recent change in therapy from an oral hypoglycemic agent to insulin. A severe occipital headache developed that was followed by lethargy, confusion and dysarthria. The results of a physical examination on admission were significant for hypothermia, a mildly elevated blood pressure and a heart rate of 64 beats per minute. Laboratory studies revealed hyponatremia and hypokalemia, and the electrocardiogram showed prominent U waves. A dilute urine was noted by urinalysis. During the hospital course he had paroxysms of hypertension and hypotension. Clinical and laboratory evidence of cardiac asymmetric septal hypertrophy was present.

This case presents a multitude of the clinical problems that are commonly encountered in the care of hypertensive patients, such as hypokalemia, acute neurologic events and paroxysmal hypertension. I will first discuss some of the pathophysiologic mechanisms that may be operating in this case, which will be followed by a discussion of the differential diagnosis. Finally, I will comment on some unanswered questions and make concluding remarks.

Paroxysmal Hypertension

The most striking feature of this case is the paroxysms of severe hypertension. One would surmise that the patient's hypertension is of relatively recent onset given the lack of signs of end-organ damage. The most common causes of paroxysmal hypertension in this setting are an excess of endogenous catecholamines and of exogenous sympathomimetic agents.[1] Included among the possible causes are pheochromocytoma, acute pulmonary edema, acute myocardial infarction, stroke, brain tumor, rebound hypertension after cessation of antihypertensive medication, hypertensive crisis associated with monoamine oxidase inhibitors, intake of sympathomimetic drugs and autonomic dysreflexia (quadriplegia). Excess catecholamines are especially likely in this case given the patient's tachycardia during the paroxysm of hypertension.

Acute Neurologic Event Associated With Hypertension

The patient's symptoms on presentation were headache with progression to confusion, lethargy and dysarthria. On physical examination there were no lateralizing signs. The differential diagnosis in this setting includes intoxications, metabolic disturbances such as hypoglycemia and hyponatremia, systemic infection, endocrine abnormalities such as thyrotoxicosis, circulatory collapse from a variety of causes, seizure, hyperthermia or hypothermia, concussion, hypertensive encephalopathy and a subarachnoid hemorrhage. Systemic infection, circulatory collapse and concussion are not suggested by this patient's clinical presentation. Intoxications, metabolic disturbances, endocrinologic causes and hypothermia will be considered later.

This patient's presentation suggests a ruptured saccular aneurysm. Defects in the arterial media and elastica are responsible for aneurysmal dilatation, which usually occurs in arteries comprising the circle of Willis or its branches. A ruptured saccular aneurysm may present in several ways, and certainly this patient's presentation of a severe headache followed by partial or complete loss of consciousness without lateralizing signs is consistent with this diagnosis. Nuchal rigidity, subhyaloid hemorrhages of the retinal vessels and bilateral Babinski's signs are absent, however. Patients with congenital polycystic disease of the kidney and coarctation of the aorta have an increased incidence of saccular aneurysms. Computed tomography (CT) and examination of the cerebrospinal fluid are helpful in making a diagnosis.

In a patient such as this with paroxysms of hypertension, hypertensive encephalopathy is certainly a consideration. This syndrome commonly presents with headache as the initial complaint, followed by lethargy, stupor, coma, seizures, visual impairment, nausea and vomiting. MacKenzie and colleagues have evaluated the effect of acute changes in arterial blood pressure on cerebral blood flow in cats.[2] These studies show that there is an autoregulatory phenomenon governing cerebral blood flow. As arterial pressure is reduced, progres-

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sive dilation of the cerebral blood vessels occurs and, as flow through the cerebral vessels increases, vasoconstriction ensues. When the mean arterial pressure reaches 180 mm of mercury, however, the vessels dilate with consequent increased cerebral flow and hyperperfusion of the brain. Cerebral edema follows with resultant hypertensive encephalopathy. Patients with chronic hypertension who have structural thickening of the vasculature appear to be more resistant to this failure of autoregulation than patients with a normal blood pressure. Any primary or secondary causes of hypertension can result in malignant hypertension with hypertensive encephalopathy. The most common cause of hypertensive encephalopathy is essential hypertension, which occurs in more than 90% of the hypertensive population. Of the secondary causes of hypertension, encephalopathy is more commonly seen with acute glomerulonephritis, toxemia of pregnancy, the use of monoamine oxidase inhibitors following ingestion of tyramine, the use of sympathomimetic drugs, renovascular hypertension and pheochromocytoma.[3]

Hypertension and Hypokalemia

In about 10% of patients who take thiazide diuretics for hypertension, hypokalemia will develop.[4] The overwhelming majority of patients with hypertension who have hypokalemia are on thiazide diuretic therapy. Half of hypertensive patients with hypokalemia that is unprovoked by thiazide diuretics will have primary aldosteronism.[5(p300)] Other conditions in which hypokalemia and hypertension are associated include diarrhea, estrogen therapy, renovascular hypertension, accelerated or malignant hypertension, salt-wasting renal disease, licorice ingestion and excess mineralocorticoids.

Dyazide (Smith Kline & French) is a capsule composed of 25 mg of hydrochlorothiazide and 50 mg of triamterene. Although the problem of hypokalemia is reduced because triamterene is a potassium-sparing diuretic, hypokalemia is still seen and often in combination with hyponatremia. The hypokalemia induced by accelerated or malignant hypertension is felt to be due to renal ischemia with activation of the renin-angiotensin-aldosterone system.[6] Hypokalemia as a result of primary aldosteronism will be discussed later.

U Waves

The U wave follows the T wave on the electrocardiogram and usually is positive in leads in which the QRS complex is positive. The mechanism that results in a U wave is uncertain but may be a result of afterpotentials at the beginning of diastole[7] or repolarization of the Purkinje system.[8] Abnormalities of the U wave include increased voltage, U waves in leads where they are not normally seen or inversion of U waves. Hypokalemia[9] and hypothermia[10(p80)] increase the U-wave amplitude. A negative U wave is reported to be highly specific for the presence of heart disease and is associated with other electrocardiographic abnormalities in more than 90% of patients.[11]

Asymmetric Septal Hypertrophy

Asymmetric septal hypertrophy is classified under the broader heading of hypertrophic cardiomyopathy. This syndrome is characterized by asymmetric septal hypertrophy (septum to posterior wall thickness ratio of 1.3/1.0), dynamic left ventricular outflow obstruction and diastolic dysfunction.

The dynamic outflow obstruction produced with asymmetric septal hypertrophy may be the result of systolic anterior motion of the mitral leaflets and chordae tendinae, large papillary muscles or abnormal shape and reduced size of the left ventricular cavity in systole.[12] Systolic anterior motion of the mitral valve occurs with ventricular ejection when a high-velocity jet pulls the mitral valve apparatus into the left ventricular outflow tract by a Venturi effect. A crescendo-decrescendo systolic murmur and a dynamic left ventricular outflow tract gradient are produced. The dynamic obstruction can be worsened by increased left ventricular contractility, reduced left ventricular volume (preload) and decreased aortic impedance (afterload). Valsalva's maneuver or standing erect reduces the ventricular volume and increases the intensity of the murmur. In contrast, squatting (which increases ventricular volume and afterload) and isometric exercise (which increases afterload) decrease the dynamic obstruction and the intensity of the murmur. The diastolic dysfunction associated with asymmetric septal hypertrophy is the result of decreased compliance of the left ventricle. This elevates ventricular pressures, which in turn causes pulmonary congestion and the most common symptom of hypertrophic cardiomyopathy, breathlessness.[13]

Hypertrophic cardiomyopathy has been found in association with lentiginosis (the diffuse presence of multiple small dark brown macules) and other disorders of neural crest tissue including pheochromocytoma.[14(p1310)] A similar hemodynamic pattern has been found in infants of diabetic mothers[15] and in patients with Friedreich's ataxia.[16] In addition, aberrant catecholamine function in a developing embryo heart has been implicated in the abnormal orientation of myofibrils seen in hypertrophic cardiomyopathy.[17]

Differential Diagnosis

Although essential hypertension is the most common cause of accelerated or malignant hypertension, this patient's paroxysms of hypertension are not consistent with this diagnosis. Likewise, this patient's presentation makes chronic renal disease, coarctation of the aorta and, especially, oral contraceptive-induced hypertension unlikely.

Renovascular Hypertension

In a recent study approximately 1% of adults with hypertension were found to have functionally significant renovascular disease.[18] When a group of patients with surgically cured renovascular disease was compared with a carefully matched group with essential hypertension, the presence of an abdominal bruit was the only clear discriminator.[19] The bruit was heard over the flank in 12% of patients with renovascular hypertension compared with 1% of patients with essential hypertension. Bruits in the epigastrium usually reflected stenosis of the celiac artery. A high-pitched systolic and diastolic abdominal murmur radiating laterally is strong evidence of significant renal artery stenosis. Patients with renovascular hypertension tend to have a shorter duration of hypertension and are usually 50 years of age or older. In addition, grade 3 or 4 funduscopic changes, a blood urea nitrogen level greater than 20 mg per dl and hypokalemia tend to be more common in patients with renovascular hypertension.

Several features of this case do not suggest renovascular hypertension. This patient was black and persons of this race have a low incidence of renovascular hypertension.[19] No bruit or funduscopic changes were noted, and paroxysmal hypertension is not characteristic of this disease.

Cushing's Syndrome

This syndrome is caused by an excess of glucocorticoids. Hypertension is present in 80%[20] and may be severe, with diastolic blood pressures greater than 130 mm of mercury.[21] Hypertension may be the result of the salt-retaining action of high levels of glucocorticoid,[22(p714)] increased production of mineralocorticoids usually seen with adrenal tumors or ectopic adrenocorticotropic hormone tumors,[23] increased levels and activity of renin-angiotensin[24] and increased vascular reactivity to pressor substances.[25] Clinical features helpful in the diagnosis of Cushing's syndrome are osteoporosis by x-ray film, central obesity, generalized obesity, proximal muscle weakness (knee bend), plethora, ecchymoses and hypokalemia.[26] The presence of striae, hypertension, edema, hirsutism, oligomenorrhea and an abnormal glucose tolerance test are of little discriminatory value. Given the patient's clinical presentation, I feel the diagnosis of Cushing's syndrome is unlikely.

Primary Aldosteronism

The clinical expression of primary aldosteronism can be related to volume expansion and hypokalemia. Hypertension in this syndrome may be severe,[27] and in one report it was suggested that a high proportion of patients with malignant hypertension have primary aldosteronism.[28]

Mineralocorticoid excess causes increased reabsorption of sodium and water and leads to volume expansion. In contrast to pathophysiologic disorders accompanying secondary aldosteronism, edema is notably absent in primary aldosteronism. The headache noted in primary aldosteronism, which is more severe, frequent and persistent than in essential hypertension, has been attributed to volume expansion. It is generally frontal rather than occipital and tends to occur in the early morning hours.

At presentation most patients have hypokalemia, but in one series as many as 22% had a normal serum potassium level.[29] Aldosterone exerts its effects in the distal tubule and collecting duct. The escape from volume expansion in primary aldosteronism involves a lesser degree of sodium reabsorption in the proximal tubule and increased sodium reabsorption in exchange for potassium in the distal tubule. There is also an exchange of sodium for hydrogen ion so that metabolic alkalosis is generated with increased proximal and distal reabsorption of bicarbonate. The clinical consequences of hypokalemia include weakness, paralysis, metabolic alkalosis, glucose intolerance and polyuria. In addition, most patients with primary aldosteronism will manifest a serum sodium level of 140 mEq per liter or greater.

A number of characteristic features of primary aldosteronism are present in this patient—that is, hypokalemia, the usual age range (30 to 50 years of age), glucose intolerance and accelerated or malignant hypertension. The patient did not have normal or increased serum sodium levels (he was receiving a diuretic, however), metabolic alkalosis, weakness and polyuria. Also, paroxysmal hypertension and tachycardia are not typical of primary aldosteronism.

Brain Tumor

A review of the literature by Bell and Doig shows 27 reported cases of paroxysmal hypertension associated with an intracranial tumor.[30] Hypothalamic compression due to suprasellar extension of pituitary chromophobe adenomata can cause striking changes in heart rate and blood pressure. Clinical features of brain tumors suggestive of pheochromocytoma were headache, tachycardia, excessive sweating, anxiety, tremor, nausea and vomiting. Localizing neurologic signs were initially absent in 5 of 27 patients, cerebrospinal fluid pressure was elevated in 73% and hypothermia occurred in one patient. Three patients had increased urinary catecholamine levels.

This patient's presentation is consistent with a brain tumor as the cause of paroxysmal elevation of blood pressure, but one would expect some premonitory symptoms and signs, papilledema or localizing neurologic signs in most patients presenting with this diagnosis. Also, we presume the patient's sensorium and body temperature must have improved during the hospital stay; otherwise, he could not have done Valsalva's, handgrip and squatting maneuvers. This implies a transitory nature to the altered state of consciousness, which would be uncommon with an intracranial tumor.

Pheochromocytoma

Pheochromocytoma can be asymptomatic or present with dramatic symptoms and signs. Commonly encountered symptoms and signs include hypertension, which may be sustained, paroxysmal or both; headache; sweating; palpitations with tachycardia or arrhythmias; weight loss; pallor; nausea; tremor; anxiety, and abdominal discomfort. The type of catecholamine that is predominantly secreted to a large extent determines the symptoms and signs.[31] Predominantly norepinephrine-secreting tumors are associated with symptoms of α-adrenergic stimulation: systolic and diastolic hypertension and reflex bradycardia. In the rare epinephrine-secreting tumors, β-adrenergic stimulation is more common: systolic hypertension, hyperglycemia, anxiety, shortness of breath and sometimes even periods of hypotension. In the very rare dopamine-secreting tumors, the presentation is one of a normal blood pressure or hypotension, tachycardia, diarrhea, polyuria and nausea. Most pheochromocytomas predominantly secrete norepinephrine with lesser contributions of epinephrine and dopamine.

Certain features of this case are in keeping with the diagnosis of pheochromocytoma. Both hyperglycemia and hypoglycemia are associated with catecholamine-secreting tumors. Neurologic events as a result of paroxysms of hypertension are common and include nonfocal disorders such as hypertensive encephalopathy, seizures and subarachnoid hemorrhage. Asymmetric septal hypertrophy is associated with pheochromocytoma. Paroxysms of hypertension are characteristic of catecholamine-secreting tumors. Likewise, hypotension is commonly noted with pheochromocytomas, but in this case hypotension may be related to a contracted intravascular volume and the use of verapamil with its potent vasodilating and negative inotropic properties. In addition, the response to β-adrenergic blocking agents like metoprolol, which allows unopposed α-adrenergic stimulation and exacerbation of hypertension, is characteristic of pheochromocytoma. The use of digoxin for the treatment of the patient's

rapid heart rate probably represents treatment of a paroxysmal supraventricular tachycardia (such as atrial fibrillation), which is also frequently noted with catecholamine-secreting tumors. Lest we become too confident of the diagnosis of pheochromocytoma, however, the literature shows us that only 50% of patients suspected of having pheochromocytomas actually have the disease.

In this patient, symptoms typical of pheochromocytoma that are absent include sweating, weight loss, pallor, nausea, tremor, anxiety and abdominal discomfort. Also, hypothermia cannot be explained by pheochromocytoma alone. A recent review of the causes of hypothermia lists a diverse group of diseases.[32] Included in this list are brain tumor, seizure and hypoglycemia, all of which are possibilities in this patient. I suspect, however, that the patient's altered sensorium was a result of hypertensive encephalopathy with or without a seizure that resulted in aberrations of thermoregulation and the hypothermia observed.

Other Causes of Hypertension

A large number of other possible causes of hypertension has been described. These include congenital adrenal hyperplasia (C-11 hydroxylase deficiency and 17-hydroxylase deficiency), hypothyroidism, hyperthyroidism, hyperparathyroidism, acromegaly, carcinoid syndrome, porphyria, psychogenic hyperventilation, burns, acute pancreatitis, alcohol withdrawal, sickle cell crisis, post-cardiopulmonary resuscitation, postoperative hypertension, polycythemia, the syndrome of inappropriate antidiuretic hormone secretion and posttransfusion. None of these are consistent with the patient's presentation.

Hypoglycemia as the cause of hypertension is a possibility given the patient's change in mental state and recent change in diabetic therapy. If this were the case, however, one would expect a low admission serum glucose level and a response in mental state to an infusion of 50% glucose solution. In addition, unless the patient's hypoglycemia remained uncorrected, one would not expect the hypertension to be paroxysmal and protracted while the patient was in hospital.

A variety of drugs, foods and poisons may cause hypertension. Included in this list are licorice (glycyrrhizic acid), phenylpropanolamine hydrochloride, phencyclidine hydrochloride, food high in tyramine when taken with monoamine oxidase inhibitors, ethylene glycol and lithium. There is no history that he ingested these substances, however, and a toxicology screen was negative.

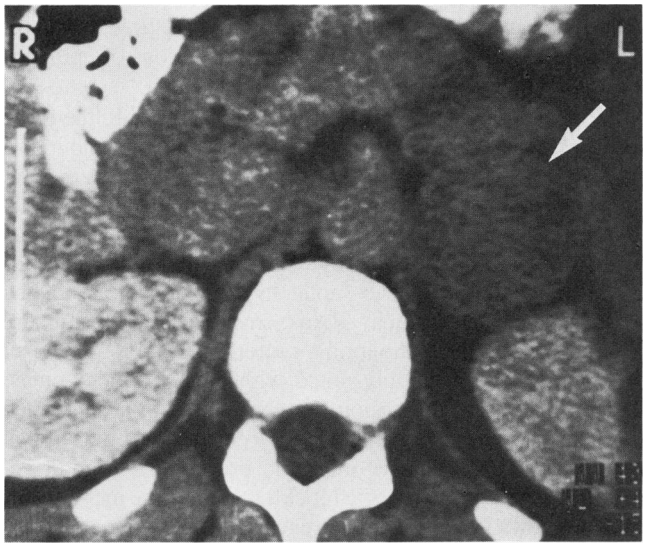

Figure 2.—A computed tomographic scan of the abdomen with contrast. The arrow points to the left adrenal mass.

Conclusion

This patient's presentation is most suggestive of a pheochromocytoma. Other disease processes discussed are possible—renovascular hypertension, primary aldosteronism, Cushing's syndrome, hypoglycemia and ingestion of a sympathomimetic drug—but not likely. The possibility of brain tumor causing this syndrome is intriguing from a pathophysiologic standpoint but, as mentioned, the absence of premonitory symptoms, papilledema or localizing signs and the transitory nature of the patient's mental state changes are against this diagnosis.

Diagnostically, I would do a spot urine analysis for metanephrines because this is the best screening procedure for pheochromocytoma and this catecholamine metabolite is least affected by interfering substances.[33] Results from a single voided urine specimen correlated closely with those found on a 24-hour urine specimen. The finding of normal urine catecholamine levels during a paroxysm of hypertension excludes pheochromocytoma. Plasma catecholamines can be measured by a radioenzymatic technique or liquid chromatography with electrochemical detection but are reported to have 20% false-negative values.[34] Administering clonidine hydrochlo-

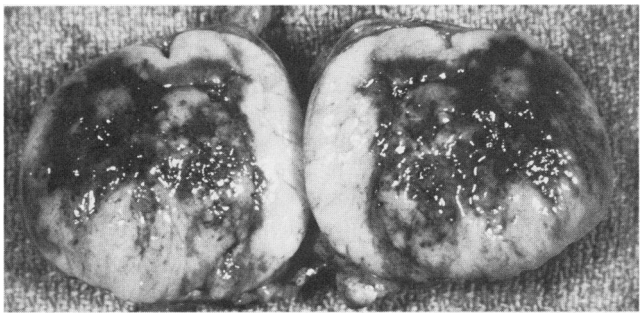

Figure 3.—The gross surgical pathologic specimen shows intraparenchymal hemorrhage.

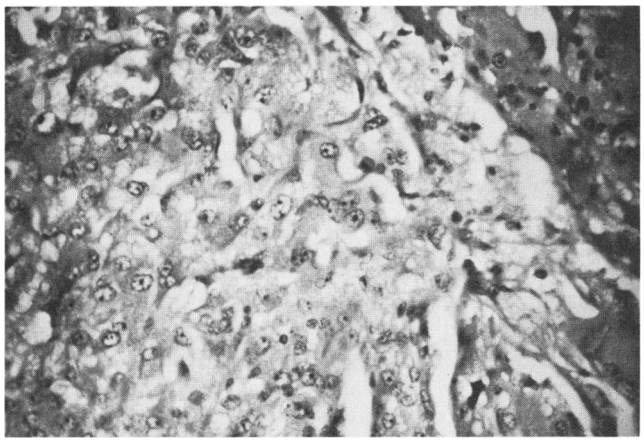

Figure 4.—Microscopic examination of the left adrenal mass shows a chromaffin cell tumor (hematoxylin-eosin stain, magnification x 125).

ride will suppress plasma catecholamines in those patients without a pheochromocytoma but will not suppress catecholamines in those patients with a tumor.[35] Finally, pheochromocytoma can usually be adequately localized by CT scan, and other procedures such as intravenous pyelogram or aortography are rarely needed.

Clinical Course

DR ENG: Urinary metanephrine and vanillylmandelic acid levels were 18,614 μg per 24 hours (normal 0 to 1,000) and 41.8 mg per 24 hours (normal 2 to 10), respectively. The plasma norepinephrine level was 21,760 pg per ml (normal 110 to 410) and the plasma epinephrine level was 12,200 pg per ml (normal <50). Plasma levels of dopamine were not elevated. A CT scan of the abdomen showed a 4-cm left adrenal mass (Figure 2). Before the surgical procedure the patient's blood pressure was controlled with the administration of phenoxybenzamine hydrochloride and propranolol. At the operation a mass was found superior to the left kidney (Figure 3) that on pathologic examination showed a chromaffin cell tumor consistent with pheochromocytoma (Figure 4). Mild diastolic hypertension was noted postoperatively, but results of a 24-hour urine collection for metanephrines and vanillylmandelic acid were within normal limits. Echocardiograms done five months after the operation showed normalization of left ventricular dimensions with a septal thickness of 1.0 cm and a posterior wall thickness of 1.0 cm.

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